REMARKS

I. Amendments to the Claims

Claims 1-15 are pending in this application. Claims 16-24 are withdrawn. Claim 1 has been amended to recite "rapidly dispersing microgranules consisting essentially of ..." Support for this amendment can be found throughout the specification, for example at paragraphs [0018]-[0019], and [0027]. No new matter has been added by reason of this amendment.

Additionally, Applicants respectfully submit that the subject matter of the amended claims would have been encompassed by the Examiner's previous search, and thus raises no new issues. Accordingly, Applicants request entry of the amendments to claim 1.

II. Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-15 under 35 U.S.C. §103(a) as allegedly obvious over *Gowan* (US 5,876,759) in view of *Ohta* (EP 0914818) and *Guo* (US 2004/0068000). Applicants respectfully submit that the cited references do not support a *prima facie* case of obviousness because they fail to teach or suggest the presently claimed invention, and therefore respectfully request that the rejection be withdrawn.

The claimed tablet rapidly disintegrates in the oral cavity and comprises at least two types of granules compressed together: (a) rapidly dispersing microgranules (RDMs) consisting essentially of a sugar alcohol or a saccharide, or a mixture thereof, having an average particle size not more than about 30 microns, ***and*** a disintegrant, and (b) "taste-masked microcapsules" prepared by encapsulating a wet milled, "granulated mass" containing "at least one drug" and "at least one polymeric binder".

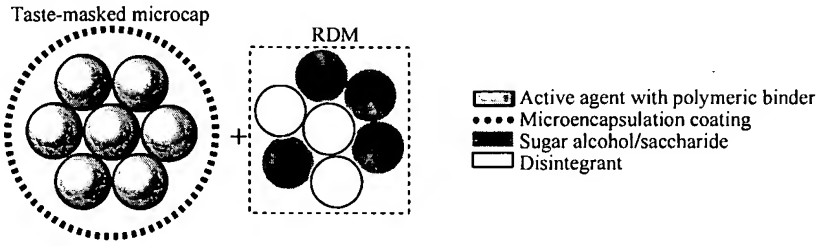
Thus, the taste-masked microcapsules of the claimed invention are agglomerates comprising "at least one drug" and "at least one polymeric binder", and by virtue of the wet milling process, possess different physical properties compared to drug particles prepared by other methods – e.g., are "hard, flexible, [and] less friable" and do not have the undesirable levels of "fines" which result from dry milling.[1] In addition, the RDMs of the claimed

[1] Present specification, ¶ [0015].

invention are agglomerates consisting essentially of "not more than about 30 micron" sugar alcohol and/or saccharide and a disintegrant. (*See* Figure 1, below, which shows an embodiment of the claimed invention.)

Embodiment of Claimed Invention: Taste-Masked Microcapsules and RDM

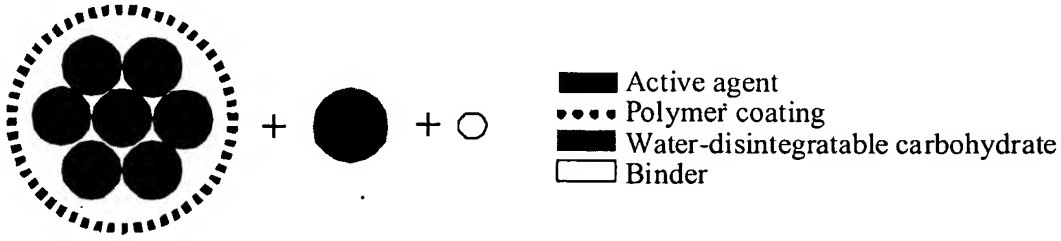
FIGURE 1



Gowan

Gowan describes a compressed, orally disintegrating dosage form prepared by dry-blending: (a) drug particles having a taste-masking coating; (b) a water-disintegratable, compressible carbohydrate; and (c) a binder. (*See* Figure 2, below). *Gowan* explains that "[t]he ingredients are dry blended and then compressed into a mass, preferably a wafer." (Col. 3, lines 2-5). Thus, *Gowan*, discloses a tablet comprising at least ***three*** separate types of particles: taste-masked drug particles, a compressible carbohydrate, and a binder. Applicants note that the required binder component of *Gowan* is *external* to the taste-masked drug particles, instead of *within* the taste-masked drug particle as in the claimed invention. Further, *Gowan* fails to disclose any information regarding friability or levels of fines for the drug particles.

FIGURE 2



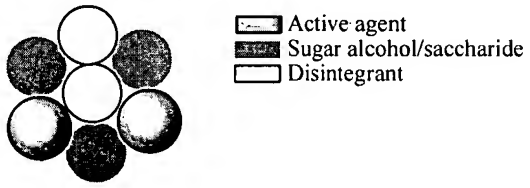
As can be seen in Figure 2, *Gowan* fails to disclose the RDMs of the claimed

invention (which are agglomerates of the constituent sugar alcohol and/or saccharide particles and disintegrant particles). *Gowan's* invention instead relies on only the "water-disintegratable, compressible carbohydrate" (col. 3, line 1) to provide for disintegration in the oral cavity and "facilitate breakup of the dosage form" (col. 3, lines 18-19). Furthermore, *Gowan* fails to even disclose excipients known in the art as disintegrants, such as crospovidone, so *Gowan* cannot reasonably even suggest particles comprising a disintegrant. In short, *Gowan* fails to teach or suggest the RDM of the claimed invention.

Ohta

Ohta describes tablets comprising a single type of drug-containing granule, prepared by granulating together a sugar alcohol or saccharide, a disintegrant, and ***a drug***, which are then compressed into a rapidly disintegrating tablet (Figure 3, below). *Ohta* fails to disclose any coating – taste-masking or otherwise – on the drug-containing granule.

FIGURE 3



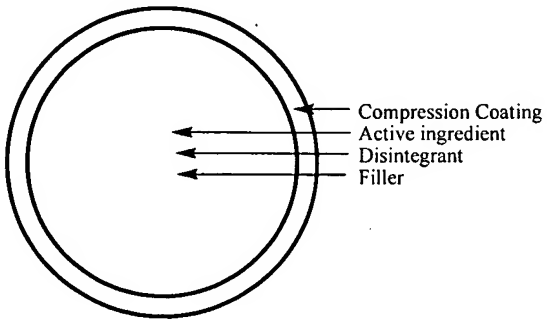
As can be seen in Figure 3, *Ohta* fails to teach either the RDMs or drug-containing granules having a taste-masking coating as in the claimed invention. While *Ohta* teaches a granule that incorporates a sugar alcohol or saccharide and a disintegrant, the granule also incorporates an active agent, which is excluded by the "consisting essentially of" language of claim 1. Further, *Ohta* fails to disclose drug particles that are microencapsulated or otherwise taste-masked. Applicants submit that since the drug-containing granules of *Ohta* are prepared by granulating a mixture of drug, sugar alcohol/saccharide, and disintegrant, at least some of the drug would be exposed on the surface of such granules, and thus would be exposed in the oral cavity upon administration.

Guo

Guo describes a "compression coated solid dosage form"[2] (*i.e.*, tablet) for oral administration that comprises a core prepared by compressing a mixture of a "bitter or unpleasant tasting" active, along with excipients such as fillers (*e.g.*, lactose, microcrystalline cellulose, etc.), and disintegrants (*e.g.*, croscarmellose sodium)[3], then coated with a compression coating having a thickness "of 0.1 mm to 5 mm." (*See* Figure 4, below). Applicants note that the compression coating of *Guo* covers the *entire* dosage form (i.e., tablet), not the individual drug-containing granules comprising the tablet as required by the claimed invention, and *Guo* fails to disclose separate particles which are agglomerates of a sugar alcohol and/or saccharide and a disintegrant.

In addition the "compression coated solid dosage form" of *Guo* is clearly designed to be swallowed whole, and not disintegrate in the oral cavity, as for the claimed invention, because disintegration of the compression coating in the mouth would cause the "bitter or unpleasant tasting" active to be released, and thus defeat the taste-masking feature of the compression coating.

Figure 4



Thus, *Guo* describes a taste-masking coating over an entire tablet, and thus fails to disclose: (a) individually taste-masked particles comprising the combination of a drug and a binder; and (b) rapidly dispersing granules comprising the combination of ≤ 30 μm sugar alcohol or saccharide particles and a disintegrant. Furthermore, *Guo's* fails to disclose the orally disintegrating tablets of *Gowan*, *Ohta*, and the claimed invention.

[2] US 2004/0068000, ¶ [0006] (hereinafter "*Guo*").

Combined References

The Examiner suggests that it would be obvious to combine the cited references to provide the claimed invention. Applicants respectfully disagree for the following reasons:

A lack of *prima facie* obviousness because none of the references disclose the claimed RDM or improved properties of the claimed invention (i.e., "not more than 15% fines" limitation of claim 3);

The combined references fail to provide sufficient direction to reasonably suggest their combination in the manner proposed by the Examiner; and

The Examiner has engaged in impermissible hindsight in order to construct the claimed invention from the references.

1. Lack of *Prima Facie* Obviousness

a. Claims Generally

As discussed above, the claimed tablet comprises at least two particles: RDMs consisting essentially of a sugar alcohol and/or saccharide in combination with a disintegrant, and taste-masked microcapsules comprising at least one drug and at least on polymeric binder (prepared by wet milling and microencapsulation).

However, *Gowan* describes a composition in which oral disintegration is provided by a "compressible carbohydrate," alone. Furthermore, *Gowan* does not even disclose disintegrants, and thus cannot teach or suggest the RDMs of the present invention, which require a disintegrant component.

Ohta only describes compositions comprising a single, drug-containing particle, whereas the claimed RDM cannot include a drug.

Guo describes a tablet core prepared by compressing a blend of drug and excipients, and does not disclose a single constituent agglomerate of a sugar alcohol/saccharide and disintegrant. Furthermore, since *Guo's* tablet is not intended to rapidly disintegrate in the oral cavity, *Guo* reasonably could not suggest the RDMs of the present invention, which provide for rapid disintegration in the mouth.

Therefore, as each of the references individually fail to teach the RDM of the claimed

[3] *Guo* at p. 3, Example 1.

invention, the combination of the cited references necessarily fails to teach or suggest RDMs, and thus fails to support *prima facie* obviousness.

Applicants therefore request that the rejection be withdrawn.

b. Claim 3

Applicants also respectfully submit that the Examiner has not established a *prima facie* case of obviousness with regard to claim 3. Claim 3 recites "said microgranule exhibiting not more than 15% fines (passing through 140 mesh screen) when tested in accordance with the procedure for friability test." As the specification notes at [0066], "granules must have the property of maintaining their integrity during handling and processing . . . [and] should exhibit sufficient strength and sufficiently low friability to withstand attrition during the handling or processing, such as microencapsulation."

None of the references cited disclose this property of reduced fines of claim 3, or provides for granulation and wet milling of a mixture comprising a drug and a binder to provide drug-containing microgranules having such properties. Furthermore, since properties such as friability are reasonably dependent on composition and processing conditions, such properties are reasonably not necessarily (i.e., inherently) present in the compositions of the cited references.

As each of the references individually fail to teach this limitation of claim 3, the combination of cited references necessarily cannot cure this deficiency, and thus fails to support *prima facie* obviousness in regard to claim 3.

Applicants therefore request that the rejection be withdrawn.

2. No Motivation to Combine the References as Proposed

The Examiner suggests that one skilled in the art would have been motivated to combine the compressed dosage forms of *Gowan* with the sugar alcohol or saccharide granules of *Ohta* to provide a rapidly disintegrating tablet according to the presently claimed invention. The Examiner argues that the motivation for the combination would have come from the desire to reduce the undesirable taste or bitterness of the *Gowan* tablet and to provide a pleasant taste perception.

However, as discussed above, Applicants note that the particles of *Ohta* are not taste-masked. Applicants submit that one would not reasonably combine the taste-masked particles of *Gowan* with the non-taste-masked particles of *Ohta*, because to do so would defeat the intent of *Gowan* to provide taste-masked compositions which can be used for "pharmaceuticals having an objectionable taste."[4]

Moreover, even if, for example, *Gowan*, *Ohta*, and *Guo* were combined, there are many different equally reasonable combinations which would not provide the claimed tablet. For instance, one reasonable combination would be, as the Examiner suggests, to simply add the sugar alcohol or saccharide of *Ohta* to the three-part compression dry-blend of *Gowan*. The resulting tablet would simply be a compressed four-component dry-blend, and would still not include the RDMs of the claimed invention, which are agglomerates of at least a sugar alcohol/saccharide and a disintegrant. Alternatively, the taste-masked drug-containing particle of *Gowan* could replace the drug particles of *Guo*, or the compression coating of *Gowan* could be used to provide taste-masking for the tablets of *Ohta*. The former combination would still lack the RDMs of the claimed invention, and the latter would lack individually taste-masked drug-containing microcapsules of the claimed invention. Thus, none of these equally reasonable combinations of the cited references would provide the claimed invention.

Moreover, elements within each of the references suggest combining the cited references in a manner leading away from the claimed invention. For example, rather than suggesting the necessity of a RDM particle comprised of a disintegrant and a sugar or sugar alcohol, *Gowan* implies that a disintegrant is wholly unnecessary in an orally disintegrating tablet (ODT) formulation, since *Gowan* does not even mention disintegrants, and teaches that oral disintegration can be provided using only a "compressible carbohydrate" component (which also lacks the ≤ 30 μm particle size of the sugar alcohol or saccharide component of the claimed rapid releasing microgranules). Further, *Ohta* teaches tablets comprising a single type of particle including all of the constituent components of the tablet, in which the drug-containing particles are not taste-masked. Finally, *Guo* suggests that taste-masking can be achieved by encapsulating the entire tablet in a compression coating rather than providing

[4] *Gowan*, col. 3, lines 13-14

individually taste-masked drug-particles microcapsules as described in the claimed invention. (In addition, use of *Guo's* compression coating would reasonably prevent such tablets from rapidly disintegrating in the oral cavity as in the claimed invention). Thus, the cited references as reasonably direct to tablets lacking RDMs (*Gowan*), tablets lacking taste-masking entirely (*Ohta*), or non-orally disintegrating tablets lacking individually taste-masked drug-containing microparticles (*Guo*).

Since the references themselves do not direct one to the particular combination suggested by the Examiner, and indeed as reasonably could be combined in a manner which would not provide the claimed invention, Applicants submit the Examiner has improperly used hindsight knowledge of Applicants' invention in proposing the asserted combination of the cited references. Accordingly, Applicants request that the rejection be withdrawn.

3. Rejoinder of Claims 16-24

Applicants respectfully submit that the withdrawn claims recite all of the limitations of the pending claims under examination. For example, independent claim 16 recites a method for preparing a tablet that disintegrates in the oral cavity, prepared by granulating, wet milling, and microencapsulating a pharmaceutically acceptable formulation comprising at least one drug; preparing rapidly dispersing microgranules comprising a sugar alcohol or saccharide having an average particle size of not less than 30 μm, and a disintegrant; and compressing the drug-containing particles and rapidly releasing granules to form a tablet from which not less than 60% of the drug dissolves in about 60 minutes. The remaining withdrawn claims all depend from claim 16, directly or indirectly, and thus include these limitations. Since, for the reasons discussed above claims 1-15 are allowable, the withdrawn claims should be rejoined.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-1283. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. 1.136(a)(3).

Dated: August 19, 2010

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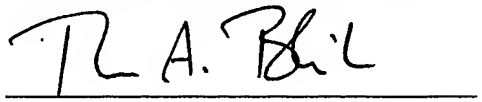
By: 

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